REMARKS

Applicants thank Examiners Choi and Pak for their time to conduct in-person and telephonic interviews on December 12, 2002 (hereinafter "the In-Person Interview"), and December 23, 2002 (hereinafter "the Telephonic Interview), respectively. The Office Action dated July 20, 2002 was discussed during the interviews. Applicants appreciate the Examiners' time and guidance as to what would be required to overcome the rejections of record. Should the present submission be non-persuasive in any way, the Examiners are kindly asked to telephone the undersigned.

Claims 42 to 47, 50, and 53 to 89 are now pending in the application, claims 48, 49, 51 and 52 having been cancelled and new claims 70 to 89 added by the above amendment. As requested by Examiner Choi during the Telephonic Interview, applicants have amended claims 42, 57, 58, and 60 to 64 to recite administering to the patient a "therapeutically effective amount" of a composition comprising carbon monoxide. Support for this amendment can be found throughout the specification. Applicants have also amended claim 42 such that the amended claim does not recite Alzheimer's disease, Parkinson's disease (which are both recited in new claim 89), primary pulmonary hypertension, and secondary pulmonary hypertension. Support for new claims 70 to 89 can be found throughout the specification, e.g., at page 21, Table 1; page 5, lines 11 to 17; page 16, lines 23 to 25; and page 16, line 20, to page 17, line 6. The amendments and new claims add no new matter to the present application.

I. Rejections under 35 U.S.C. § 112, first paragraph

Claims 42 to 69 were rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement because, according to the Office Action (at page 2):

> [The specification] does not reasonably provide enablement for treatment of any and all patients, including humans, oxidative stress in general, the list of conditions or disease states set forth in Claims 42-52, 57, 58, 60-69, or inflammation in general, including inflammation of the kidneys, brain, heart, liver, spleen, skin and lungs or secondary to sepsis.

Further, the Office Action states (at page 2):

> The claimed invention does not appear to be currently recognized as a treatment for the various conditions and disease states in humans. Further, the working

> examples are limited to rats and the effects are observed either in lungs or on single cells, i.e., muscle cells or macrophages. It is asserted that the methods will treat a wide range of conditions and/or disease states; however, the disclosure does not appear to indicate what exactly is being treated, i.e., symptoms, underlying mechanisms, underlying disease, secondary problems associated with underlying disease, etc. Further, the conditions and disease states listed are in many cases not a specific disease but represent a broad category of a number of disease having different etiologies, symptoms and/or treatments. Also, it appears that the active compounds are inhaled, however, other than the lungs there does not appear to be set forth in the disclosure how the compounds, in therapeutically effective amounts, reach the intended site be it kidneys, brain, heart, liver, spleen, skin, or systemically in general.

Applicants respectfully traverse this rejection for the following reasons. First, regarding the treatment of patients, applicants submit that the specification is sufficient to enable a skilled practitioner to practice the invention in patients other than those used in the examples. Applicants sought to demonstrate carbon monoxide treatment in *in vivo* models widely accepted in the art as correlating to treatment in other animals. Few *in vivo* models are as widely accepted as rat and mouse models. As would any skilled practitioner, applicants used these models to demonstrate the effectiveness of carbon monoxide treatment *in vivo*. Applicants therefore acknowledge the Office Action's statement that "the specification is enabling for the treatment of rats having the disease states and/or conditions specifically treated." However, in using the rat (or mouse) model, applicants sought to demonstrate that such treatment could be carried out in live animals in general, not just in rats (or mice). Given that (1) these models are widely accepted, and (2) the specification is enabling for the treatment of rats, the specification would clearly enable a skilled practitioner to treat other animals, e.g., humans, using carbon monoxide. The Office Action, on the other hand, appears to suggest that every animal species covered by the claims would have to be treated in a working example in order to provide enablement for the treatment of those animals. Such a showing is, of course, not required by law (see MPEP §2164.02, discussed in further detail below). All that is required is sufficient evidence to overcome any bias in the art that a claimed method would not work. As established by the Federal Circuit in *In re Brana* (51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed Cir. 1995)), even *in vitro* results can suffice for this purpose. In supplying *in vivo* results in two different animal models, applicants have more than met their burden here.

Second, applicants submit that the specification demonstrates that inhaled carbon monoxide can be effective for treatment of disorders other than those involving the lung. In this Office Action, it was suggested that the specification is non-enabling because it allegedly lacks evidence that inhaled carbon monoxide reaches parts of the patient other than the lungs, in therapeutically effective amounts. In fact, at pages 31 to 32 (directly under the heading "CO selectively targets both pro-inflammatory and anti-inflammatory cytokines *in vivo*"), the specification provides direct evidence that inhaled carbon monoxide has system-wide effects. In this example, lipopolysaccharide (LPS) was injected intraperitoneally into mice to induce systemic inflammation, in the presence or absence of inhaled carbon monoxide. Serum was harvested and analyzed for TNF- α by ELISA (see page 28 of the specification). Applicants observed that inhaled carbon monoxide attenuated LPS-induced TNF-α (a pro-inflammatory cytokine) production and augmented IL-10 (an anti-inflammatory cytokine) levels *in vivo*, indicating that inhaled carbon monoxide exerted potent systemic anti-inflammatory effects in the mice. Applicants submit that this example demonstrates clearly that inhaled carbon monoxide has systemic effects and can be expected to be effective for treatment of disorders involving organs other than the lung. Further evidence that inhaled carbon monoxide reaches parts of the patient other than the lungs is provided below in applicants' specific examples of diseases successfully treated with carbon monoxide.

Third, applicants submit that the specification is enabling for the treatment of all of the diseases and conditions recited in the present claims. Most of the conditions are known to be causally linked to oxidative stress and/or inflammation. The specification provides working examples demonstrating that inhaled carbon monoxide can, in fact, be used to treat oxidative stress and inflammation. For example, the present application provides data demonstrating that inhaled carbon monoxide provides increased tolerance to lethal levels of hyperoxia, which is a clinically relevant model of oxidative stress (see general discussions of this model in, e.g., Lee et al., Am. J. Respir. Cell Mol. Biol. 14: 556-568 (1996), appended hereto as Exhibit A; and Otterbein et al., Am. J. Physiol. 276: L688-L694 (1999), appended hereto as Exhibit B). This model provides support for applicants' claims directed to treatment of conditions involving oxidative stress, and in particular, to treatments for the lung diseases recited in claims 42 to 47, 50, 53 to 59, 62, 63 and 69 to 74. Further, the specification provides a working

example demonstrating that carbon monoxide is a potent anti-inflammatory agent, both *in vitro* and *in vivo*, using the widely-employed model of LPS-induced inflammation (see general discussions of this model in, e.g., Otterbein et al., Nat. Med. 6(4): 422-429 (2000), appended hereto as Exhibit C)). This model supports applicants' claims directed to treatments for inflammation, e.g., to treatment of inflammatory conditions recited in claims 62 to 64, and in particular to treatment of sepsis and/or inflammation associated with sepsis (claims 65 and 67). Again, applicants note the Office Action's statement that "the specification is enabling for the treatment of rats having the disease states and/or conditions specifically treated." Given that (1) the models used in the specification are art-recognized as correlating generally to oxidative stress and inflammation conditions, and (2) the Examiner recognizes that the specification is enabling for the treatment of these conditions in rats, applicants submit that the specification would enable a skilled practitioner to treat the conditions recited in the claims, e.g., oxidative stress and inflammation and conditions involving oxidative stress and inflammation, in patients such as humans. The Office Action cites no evidence to the contrary.

In addition to applicants' comments above, and as requested by Examiners during the In-Person Interview, applicants describe below several examples of conditions successfully treated with carbon monoxide administered by inhalation as described in the present specification. These examples are derived from publications and patent applications dated subsequent to the priority date of the present application, but show that the specification as filed provides full enablement for the pending claims. They further prove that: (1) as taught in the present specification, conditions associated with oxidative stress, inflammation, and/or unwanted cellular proliferation can be treated with inhaled carbon monoxide; and (2) carbon monoxide reaches parts of the body other than the lungs, e.g., intestines, liver, and heart, in therapeutically effective amounts. Copies of the publications are attached hereto as exhibits; at the Examiner's suggestion, copies of the cited provisional applications are not enclosed, but presumably the U.S. Patent and Trademark Office files are available to the Examiner.

Example 1: Methods of Treating Necrotizing Enterocolitis (Provisional Application Serial No. 60/372,599).

This application provides data demonstrating that inhaled carbon monoxide can protect against development of necrotizing enterocolitis (NEC). NEC is a disease of newborns characterized by intestinal inflammation, gut barrier failure and intestinal necrosis. In these experiments, animals suffering from experimentally-induced NEC inhaled carbon monoxide (250 ppm) for one hour per day over a several-day period. The distal ilea were subsequently harvested from the animals. Intestinal inflammation in the distal ilea characteristic of NEC was evaluated by gross-inspection and histological analysis, and Western blot analysis was performed to evaluate expression of HO-1 and cyclooxygenase-2 (COX-2; a known inflammatory mediator associated with NEC) in the ileal mucosa. Animals treated with carbon monoxide exhibited decreased mucosal COX-2 expression as compared to controls, indicating that carbon monoxide treatment prevents or attenuates the development of NEC. This application demonstrates that inhaled carbon monoxide reaches the gut in therapeutically effective amounts and provides another example of an inflammatory condition that can be treated with inhaled carbon monoxide.

Example 2: Carbon Monoxide Suppresses Arteriosclerotic Lesions Associated with Chronic Graft Rejection and with Balloon Injury (Provisional Application Serial No. 60/356,718)

This application provides data demonstrating that inhaled carbon monoxide can attenuate the development of arteriosclerotic lesions associated with both chronic graft rejection and intimal hyperplasia following balloon angioplasty-induced vessel injury. Intimal hyperplasia arises from vascular injury, e.g., subsequent to procedures such as angioplasty, bypass surgery, and organ transplantation. The data demonstrate that continuous inhalation of carbon monoxide (250 ppm) suppresses development of transplant associated arteriosclerotic lesions and intimal hyperplasia in transplanted aortic segments that were grafted between the renal (kidney) arteries of recipient animals. Further, inhalation of carbon monoxide (250 ppm) for 1 hour prior to balloon-mediated carotid artery injury was observed to be sufficient, with no further treatment, to suppress intimal hyperplasia. Like the model of LPS-induced inflammation described in the

specification, this application illustrates that inhaled carbon monoxide reaches parts of the body other than the lungs (here, blood vessels in the abdomen and the neck) in therapeutically effective amounts.

Example 3: Methods of Treating Hepatitis (Provisional Application Serial No. 60/381,527)

This application provides data demonstrating that inhaled carbon monoxide protects against development of hepatitis. Hepatitis is a disease characterized by inflammation of the liver and can be caused by agents such as viruses, alcohol, and other drugs. A model of immune-mediated liver injury was employed to demonstrate the efficacy of carbon monoxide for protecting against hepatitis. Specifically, TNF and D-galactosamine (D-Gal) were administered to animals to induce liver damage/failure. Subsequently, the animals inhaled carbon monoxide (250 ppm) for eight hours. This regimen of carbon monoxide treatment was observed to prevent immune-mediated liver injury. This application demonstrates that inhaled carbon monoxide can reach organs other than the lungs in therapeutically effective amounts, and in particular, supports applicants' claims directed to treatment of inflammation of those organs (e.g., claims 62, 63, and 64).

Example 4: Methods of Treating Tumor Growth and Metastasis (Provisional Application Serial No. 60/386,561)

This application provides data demonstrating that inhaled carbon monoxide increases the survival rate of animals injected with tumor cells, reduces tumor growth, and reduces angiogenesis in animals. Four *in-vivo* models were employed, three for tumor growth (two of which are mentioned here) and one for angiogenesis. One tumor growth model involved injecting animals intraperitoneally with mesothelioma (AC29) cells and monitoring the animals for overall survival. Another involved injecting animals subcutaneously with adenocarcinoma (A549) cells and monitored the animals for tumor volume. The angiogenesis model was a Matrigel™ *in vivo* angiogenesis assay, wherein a solubilized basement membrane matrix (Matrigel™) containing growth factor and heparin was implanted under the skin of mice. In the two tumor growth models, animals inhaled carbon monoxide (250 ppm) continuously for a period of six weeks. In the angiogenesis model, animals inhaled carbon monoxide (250 ppm) for

a period of two weeks. Animals that inhaled carbon monoxide in the tumor growth models survived longer and had smaller tumors than controls. Animals that inhaled carbon monoxide in the angiogenesis model exhibited less angiogenesis than controls. This application supports applicants' claims directed to treatment of cancer with carbon monoxide, e.g., claims 60 and 61. It also shows that inhaled carbon monoxide can be used to treat conditions outside the lungs, including in the abdomen and the skin.

Example 5: Treatment for Hemorrhagic Shock (Provisional Application Serial No. 60/424,804)

This application provides data demonstrating that inhaled carbon monoxide protects against organ injury in animals subjected to hemorrhagic shock (HS). HS may result from any condition associated with blood loss, e.g., internal (e.g., gastrointestinal bleeding) or external hemorrhage, and trauma (e.g., penetrating or blunt trauma), and is associated with a systemic inflammatory response. In the experiments described in this application, animals suffering from HS inhaled carbon monoxide (250 ppm) for a period of 6.5 hours (during a combined HS/fluid resuscitation period), or for a period of 24 hours. Animals that inhaled carbon monoxide exhibited decreased serum IL-6 (a pro-inflammatory cytokine) levels, increased IL-10 (an anti-inflammatory cytokine) levels, and less liver and intestinal injury compared to controls. Like the model of LPS-induced inflammation described in the specification, this application illustrates that inhaled carbon monoxide reaches parts of the body other than the lungs and has system-wide effects. Further, this example illustrates in particular that inhaled carbon monoxide reaches the liver and gut in amounts effective to treat/prevent inflammation, supporting claims 62 and 63.

Example 6: (a) Sato et al., "Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse to rat cardiac transplants," *J. Immunol.* 166: 4185-4194 (2001) (appended hereto as Exhibit D)

(b) Carbon Monoxide Improves Outcomes in Tissue and Organ Transplants and Suppresses Apoptosis (U.S. Patent Application Serial No. 10/177,930)

This publication and patent application describe a model demonstrating that inhaled carbon monoxide suppresses rejection in cardiac transplants. Briefly, mouse hearts were

transplanted into rat recipients. Donor mice inhaled carbon monoxide (250 ppm to 400 ppm) for two days prior to transplantation and recipient rats inhaled carbon monoxide (250 to 400 ppm) for 14 to 16 days. Graft rejection was suppressed in recipients that inhaled carbon monoxide compared to controls. Like the examples above, this example illustrates that inhaled carbon monoxide reaches organs other than the lungs in therapeutically effective amounts. In particular, this example illustrates that inhaled carbon monoxide reaches the heart in amounts effective to treat/prevent inflammation, supporting claims 62 and 63.

Example 7: Chapman et al., "Carbon monoxide attenuates aeroallergen-induced inflammation in mice," Am. J. Physiol. Lung Cell Mol. Physiol 281: L209-L216 (2001) (appended hereto as Exhibit (E).

This publication provides data demonstrating that inhaled carbon monoxide can be used to treat asthma, an inflammatory disease of the lungs. An aeroallergen model was employed, wherein animals were sensitized to ovalbumin and subsequently challenged with aerosolized ovalbumin. The animals inhaled carbon monoxide (250 ppm) for 2 hours prior to the aerosol challenge, and continuously inhaled carbon monoxide after the aerosol challenge. Inhaled carbon monoxide reduced inflammation in the lungs of the challenged animals compared to controls who did not receive carbon monoxide. Applicants submit that this example further supports claims reciting lung diseases, e.g., claims 42 to 47, 50, 53 to 59, and 69 to 74, and in particular supports claims reciting treatments for asthma (claims 57 to 59) and inflammation of the lung (claims 62 and 63).

The examples discussed above demonstrate that carbon monoxide is effective for treating many conditions associated with inflammation, including some involving the intestines. Applicants note for the record that in another animal model of inflammation at an intestinal site, carbon monoxide does not appear to be effective (see Provisional Application Serial No. 60/372,762). However, as the Examiner is aware, U.S. law does not require that all embodiments encompassed by a claim be operable for the claim to comply with the enablement requirement (see, e.g., *Atlas Powder Co. v. E.I duPont de Nemours & Co.*, 750 F. 2d 1569, 1576-1577, 224 USPQ 409, 414 (Fed. Cir. 1984)).

During the In-Person Interview, Examiner Choi opined that treating a patient with carbon monoxide to reduce/prevent inflammation in the brain would not treat Alzheimer's disease and Parkinson's disease. Applicants' representative explained that both of these diseases are known to involve inflammation of the brain, and referred to Potter et al. (Neurobiology of Aging 22:923-930 (2001); appended hereto as Exhibit F) and Czlonkowska et al. (Med. Sci. Monit 8(8):RA165-177 (2002); appended hereto as Exhibit G) in support of applicants' claims. These publications respectively indicate that Alzheimer's disease and Parkinson's disease involve inflammation. Both suggest treating the disease with anti-inflammatory agents (see, e.g., Potter et al. at page 923 (Abstract) and page 927, column 2 to page 928, column 1; and Czlonkowska et al. at page RA165 (Summary) and page RA174, column 1). The Examiner requested that claims reciting these two diseases be amended to recite treating inflammation associated with Alzheimer's disease and Parkinson's disease. In the interest of moving the application toward allowance, applicants have amended claim 42 to delete recitation of Alzheimer's disease and Parkinson's disease, opting instead to recite both of these diseases in new claim 89. As requested by the Examiner, claim 89 recites a method of treating inflammation associated with Alzheimer's disease and Parkinson's disease. As evidence that carbon monoxide can reach the brain of a patient in therapeutically effective amounts, applicants submit Brown et al. (J. Appl. Physiol. 68(2):604-610 (1990); appended hereto as Exhibit H), which provides evidence that inhaled carbon monoxide can enter rat brain cortex.

The Office Action further states (at page 4) that:

> As late as 1999, in a paper published by two of the inventors, the paper indicated that it may not be possible to prove that endogenous CO mediates the protective effects of HO-l in vivo and there was only a possibility that inhalation of CO would be useful in other inflammatory disease states and that further experimentation was necessary. (Otterbein et al., pg. L693).

It appears from the quoted language that the present rejection is based, in part, on an assumption that because the authors/inventors have speculated that it may not be possible to design an experiment to prove endogenous carbon monoxide (i.e., carbon monoxide produced by normal cellular metabolism *in vivo*) mediates the protective effects of the enzyme HO-1 *in vivo*

(see Otterbein et al. at page L692, column 2, para. 1), exogenously administered carbon monoxide would not be effective for treating the recited disorders. This assumption is unwarranted. Whether or not carbon monoxide produced naturally within the body by the enzyme HO-1 has anything to do with the biological effects of HO-1 was apparently of scientific interest to the authors of the paper, but has little if anything to do with the question of whether treatment with inhaled carbon monoxide can alleviate disease. In fact, in explaining what the mechanism is likely to be, applicants have supplied far more than the law requires in this regard.

Further, it appears from the quoted statement above that the Office Action rejects the claims because the authors of Otterbein et al. have speculated (at page L693, column 1, paragraph 2) that:

> Our work raises the intriguing possibility for the potential therapeutic use of low concentrations of CO in clinical settings, not only in lung disorders such as ARDS and sepsis but also in a variety of other inflammatory disease states.

Applicants fail to see how such a positive statement can be regarded in any way as denigrating the present invention. It provides no basis to conclude that clinical use of carbon monoxide is unlikely to work for any of the conditions mentioned. Nor does it suggest that undue experimentation will be necessary to make it work.

The specification provides an explanation of how carbon monoxide can be used to treat oxidative stress and inflammatory disorders, and sets forth working examples in art-recognized models. Applicants submit that this is all that is required in order to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The Manual of Patent Examining Procedure (MPEP) 2164.02 states, in relevant part:

> In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Applicants respectfully submit that the Office Action presents no evidence that the models used in the specification do not correlate to the human disease conditions described in the

specification. Given the information and examples provided in the specification, applicants submit that a skilled artisan would not need to engage in undue experimentation to make or use the invention commensurate in scope with the claims. The Examiner has cited no evidence to contradict this assertion. Thus, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

II. Rejection under 35 U.S.C. § 112, second paragraph

Claims 42 to 69 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because, according to the Office Action (at page 5):

> Claims 42-69 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The concentration of the components making up the gas does not adequately indicate how much of the therapeutic gas is being administered. In light of the toxic nature of the gases being introduced the claims should indicate rate and duration of administration and/or standardized measurement of the amount of gas administered in vivo.

During the In-Person Interview, Examiners Choi and Pak both expressed considerable concern about the dangers of inhaling carbon monoxide gas and the safety of the methods recited in the claims. Examiner Choi explained that the present rejection was related to those concerns and requested that the claims be redrafted to exclude administration of lethal doses of carbon monoxide. Applicants' representative explained that the fact that carbon monoxide, like almost all drugs, is potentially toxic in high concentrations does not mean that claims reciting its administration are indefinite without recitation of exact doses. Applicants' representative pointed out that the courts and the MPEP specifically prohibit the U.S. Patent and Trademark Office from basing a rejection on the possibility that a claimed treatment might not be "safe," such a consideration being the concern of the FDA, not the Patent Office. Further, applicants submit that there is an extensive body of literature describing the toxicity (or lack thereof) of various levels of carbon monoxide, and that skilled practitioners would be guided by the present specification and such literature in determining what doses of carbon monoxide are safe for delivery to a patient. However, in the interest of moving the present application toward allowance, applicants have amended claims 42, 57, 58, and 60 to 64, as requested by Examiner

Choi during the Telephonic Interview. As amended, these claims recite administering to a patient a "therapeutically effective amount" of a composition comprising carbon monoxide. Examiner Choi indicated that such an amendment would allay the Examiners' concerns about the safety of the claimed methods. Thus, applicants respectfully request that the present rejection be withdrawn.

III. Rejections under 35 U.S.C. § 102 and § 103

Claim 69 was rejected as allegedly anticipated by, and allegedly obvious in view of, Abidin et al. (Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina (1978) 6:63-67; an English translation was supplied by the Examiner). Abidin describes a study performed in rats to investigate the combined effects of potentially unhealthy levels of oxygen (about 40%) and low levels of carbon monoxide (about 50 ppm) on animals. As discussed during the Telephonic Interview, and in the interest of moving the present application toward allowance, applicants have amended claim 69 to recite that the patient is human. This amendment is supported throughout the specification, e.g., at page 10, lines 15 to 17. Applicants submit that Abidin does not describe identifying a human patient and administering carbon monoxide to the patient. Thus, Abidin does not anticipate amended claim 69 because it does not describe all of the limitations recited by this claim. In view of the above, applicants respectfully request that the rejection of claim 69 under 35 U.S.C. § 102 be withdrawn.

Further, applicants submit that amended claim 69 is not obvious in view of Abidin. During the Telephonic Interview, applicants' representative asserted, and Examiner Choi confirmed, that Abidin does not teach, or even suggest, administering carbon monoxide to humans (or any other animals) as a therapeutic agent for any purpose. Thus, Abidin does not render amended claim 69 obvious. Accordingly, applicants request that the rejection of the claim under 35 U.S.C. § 103 be withdrawn.

Applicants have also added claims 74 and 79 as discussed during the Telephonic and In-Person Interviews. Claim 74 recites a method of treating a human patient to reduce hyperoxic lung injury, and is supported throughout the application, e.g., at page 22, lines 1 to 13. Claim 79 recites a gaseous mixture that includes at least 98% oxygen gas and an amount of carbon monoxide effective to reduce hyperoxic lung injury caused by inhaling the oxygen gas, and is

also supported throughout the application, e.g., at page 20, line 23 to page 21, line 5. Applicants respectfully submit that claims 74 and 79, like claim 69, are not anticipated by, or obvious in view of, Abidin. Abidin does not teach, or even suggest, administering carbon monoxide to humans (or any other animal) to treat hyperoxic lung injury (or any other disease), nor does it teach or suggest a gaseous mixture that allows a patient to breath high concentrations (at least 98%) of oxygen gas. Thus, applicants respectfully request that claim 69 and new claims 74 and 79 (and all new claims that depend from each one of these claims) be allowed.

Claims 42 to 47 and 50 to 67 were rejected as allegedly obvious over WO 98/08523 (hereinafter "Eschwey") in view of Choi et al. (Am. J. Respir. Cell. Mol. Biol. Jul;15(1):9-19 (1996)), Lefer et al. (Methods and Findings in Experimental and Clinical Pharmacology, 15(9):617-622 (1993)), Vassalli et al. (Eur. Resp. J. 12, Suppl. 28, 273s (1998)), and Abidin et al. (Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 6:63-67 (1978)). Applicants respectfully traverse this rejection for the reasons discussed below.

Eschwey (English translation attached hereto as Exhibit I) describes the use of "hydrogenous medications," i.e., gaseous mixtures containing hydrogen (e.g., protium, deuterium, or tritium), for the treatment of inflammatory processes and cancer in animals. Eschwey states that hydrogen-containing mixtures have anti-tumor and anti-inflammatory activities and are therefore useful for treating cancer and various inflammatory conditions. Eschwey includes a list of other compounds that can optionally be included in the hydrogenous medications, such as "NO (nitric oxide), N_2O (nitrous oxide), acetylene (ethine, C_2H_2), ethylene (ethene, C_2H_4) or carbon monoxide (CO)" (Eschwey translation at page 7, lines 16 to 18, see also page 14, lines 20 to 24). Eschwey does not disclose, or even suggest, that carbon monoxide has anti-inflammatory or anti-tumor activity, or that it can be used to prevent or limit oxidative stress. While Eschwey provides a discussion about the uses of medications containing hydrogen or hydrogen plus nitric oxide to treat inflammatory diseases (see, e.g., page 8, line 3, to page 9, line 16, and in particular page 8, line 15 to page 9, line 5), it does not disclose, or even suggest, that carbon monoxide can be used to treat inflammation or oxidative stress, diseases associated with either of those conditions, or cancer. In fact, Eschwey does not describe specific activities of, or uses for, any of the listed optional compounds except nitric and nitrous oxide. Eschwey merely refers to the optional compounds as "pharmacologically active" gases, without

elaboration. Accordingly, a skilled practitioner would not have been motivated by Eschwey to administer carbon monoxide gas to treat the diseases and conditions recited in applicants' claims. Given Eschwey's complete lack of guidance regarding the biological activities and uses of carbon monoxide, and the generally known harmful effects of carbon monoxide at high concentrations, a skilled practitioner would have had no reason to expect such a treatment to be successful.

The Office action also cites Choi, Lefer, Vassalli, and Abidin. However, none of these additional references provides the information missing in the primary reference. Choi is a review article that describes the physiological significance of heme oxygenase-1 in lung injury caused by oxidative stress. Choi also describes the role of endogenously-produced carbon monoxide (i.e., carbon monoxide produced in the body via heme oxygenase-1 degradation of heme). Nowhere does Choi teach, or even suggest, that exogenously-delivered carbon monoxide could be used as a therapeutic agent. Thus, Choi has no bearing upon the patentability of the pending claims.

Lefer discloses *in vitro* experiments investigating the effects of nitric oxide- and carbon monoxide-saturated aqueous solutions on isolated blood vessels and leukocytes. Specifically, Lefer discloses that nitric oxide- and carbon monoxide-saturated Krebs-Henseleit solutions relax isolated rat superior mesenteric arteries (SMA) rings *in vitro*, and that these solutions attenuate adherence of cat polymorphonuclear leukocytes to cat SMA endothelium *in vitro*. Lefer does not mention the use of inhaled carbon monoxide gas for any purpose, much less as a therapeutic agent. Nowhere does Lefer even suggest that inhaled carbon monoxide gas might exert beneficial effects *in vivo*, or that it could be administered to a patient without toxic effects. Contacting pieces of blood vessels with an aqueous solution is conceptually far removed from administration of a gas into the lungs of a patient. Thus, Lefer provides no motivation whatsoever to use inhaled carbon monoxide gas as a therapeutic agent.

Vassalli is a publication cited in the Office Action because, according to the Office Action (at page 6): "Vassalli et al. (1998) teaches that carbon monoxide inhibits acute pulmonary vasoconstriction and would be effective in the treatment of acute pulmonary hypertension." Applicants have amended claim 42 to remove reference to primary or secondary acute

pulmonary hypertension. Thus, Vassalli has no bearing on the patentability of the pending claims, as amended.

As discussed above, Abidin merely describes a study performed in rats to investigate the combined effects of potentially unhealthy levels of oxygen and low levels of carbon monoxide on animals. Abidin does not teach, or even suggest, that carbon monoxide gas could be administered as a therapeutic agent to treat any of the diseases or conditions recited in applicants' claims. Thus, a skilled practitioner would not have been motivated by Abidin to use carbon monoxide gas in this fashion. In fact, Abidin even teaches away from such uses of carbon monoxide, referring to carbon monoxide as a "chemical pollutant" (see the English translation of Abidin at page 82, line 10), and undertaking the study described in Abidin to set hygienic standards for carbon monoxide (and oxygen) levels in small airtight spaces (e.g., in a spaceship).

Applicants submit that none of the publications cited in the Office Action, singly or in combination, teaches or suggests administering inhaled carbon monoxide gas as a therapeutic agent to treat the diseases and conditions recited in the pending claims. Thus, a skilled practitioner would find no motivation, nor a reasonable expectation of success, for using carbon monoxide as described in the present application in these or any other publications. For all of the reasons discussed above, applicants request that the present rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Attached is a marked-up version of the changes being made by the current amendment. Enclosed is a check for $920 for the Petition for Extension of Time fee for a three month extension. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 13681-003002.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claims 48, 49, 51, and 52 have been cancelled.

Claims 42, 57, 58, 60 to 64, and 69 have been amended as follows:

42. (Amended) A method of treating a disorder secondary to or resulting in oxidative stress to a patient, comprising:

identifying a patient suffering from a disorder secondary to or resulting in oxidative stress; and

administering to the patient an effective amount of a composition comprising carbon monoxide, wherein the disorder is selected from the group consisting of: emphysema, bronchitis, adult respiratory distress syndrome, cystic fibrosis, pneumonia, and interstitial lung disease[, primary pulmonary hypertension, secondary pulmonary hypertension, Parkinson's disease and Alzheimer's disease].

57. (Amended) A method of treating asthma in a human patient, comprising:

identifying a human patient suffering from asthma; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide.

58. (Amended) A method of treating asthma in a patient, comprising:

identifying a patient suffering from asthma; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, wherein the composition comprises about 0.0001% to about 0.25% carbon monoxide.

60. (Amended) A method of treating cancer in a patient, comprising:

identifying a patient suffering from cancer; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, wherein the cancer is selected from a group consisting of: cancer of the stomach, colon, rectum, liver, pancreas, lung, kidney, cervix uteri, corpus uteri, ovary, prostate, testis, bladder, skin, brain/central nervous system, head, neck, mouth, esophagus, larynx and pharynx; Hodgkins disease; non-Hodgkins leukemia; sarcoma; choriocarcinoma; and lymphoma.

61. (Amended) A method of treating cancer in a human patient, comprising:

identifying a human patient suffering from cancer; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, to thereby treat cancer in the patient.

62. (Amended) A method of treating inflammation in a patient, comprising:

identifying a patient suffering from inflammation of at least one organ selected from a group consisting of: kidney, brain, heart, liver, spleen, skin and lung; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, wherein the inflammation is of a type selected from a group consisting of: acute, allergic, alterative, atrophic, catarrhal, croupous, fibrinopurulent, fibrinous, immune, hyperplastic, proliferative, subacute, serous and serofibrinous inflammation.

63. (Amended) A method of treating inflammation in a human patient, comprising:

identifying a human patient suffering from inflammation of at least one organ selected from a group consisting of: kidney, brain, heart, liver, spleen, skin and lung; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, to thereby treat inflammation in the patient.

64. (Amended) A method of treating inflammation in a patient, comprising:

identifying a patient suffering from or at risk of inflammation of at least one organ selected from the group consisting of: kidney, spleen and skin; and

administering to the patient a therapeutically [an] effective amount of a composition comprising carbon monoxide, to thereby treat inflammation in the patient.

69. (Amended) A method of treating a patient to reduce oxidative stress associated with hyperoxia, comprising:

identifying a human patient suffering from or at risk for oxidative stress associated with hyperoxia; and

administering to the patient a composition comprising carbon monoxide in an amount effective to reduce oxidative stress associated with hyperoxia.